

## Spectral and electrochemical investigations of ketorolac tromethamine

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The spectral and electrochemical studies of ketorolac tromethamine, **1** are presented. **1** undergoes a single step two-electron transfer reduction in media of  $pH < 6.00$  and in a two step one-electron reduction in basic media to give a secondary alcohol. **1** is also found to act as a bidentate ligand to give **3**. Electrochemical investigations of **1** in non-aqueous media are presented. Relevant electrochemical data such as  $n$ ,  $E_{pc}$ ,  $i_{pc}$ ,  $\alpha n_a$ ,  $k^0_h$ ,  $D_0$ , etc. are reported.

Ketorolac Tromethamine, **1** is structurally related to Tolmetin and Zomepirac. It is prepared by neutralisation of  $(\pm)$ -2-benzoyl-dihydro-pyrrolizine-5-carboxylic acid with 2-amino-2-hydroxymethyl-1,3-propanediol<sup>1</sup>. It is marketed through several trade names such as Dolac, Ketanov, etc.

**1** is basically a non-steroidal analgesic drug having similar pharmaco-kinetic actions as are other non-steroidal anti-inflammatory drugs (NSAID's) in inhibiting the prostaglandin synthesis. Unlike other NSAID's, ketorolac has a stronger analgesic activity besides a moderate anti-inflammatory activity. It may cause gastrointestinal side effects, probably by reducing the synthesis and activity of prostaglandins. Spectral and electrochemical studies of the drug in aqueous media at several  $pH$ 's would provide useful information about the electron transfer characteristics of the drug which should provide an insight into its pharmaco-kinetics. No detailed electrochemical investigations of this important drug molecule are reported yet in the literature. Further, its ability to serve as a bidentate ligand through its carbonyl oxygen and pyrrolidic nitrogen, is not yet demonstrated. Prompted by its medicinal importance, its structure and dearth of reports on its electrochemistry and coordination chemistry, we studied the spectral and electrochemical characteristics of the drug in considerable detail and the results of these studies are presented here.

### Materials and Methods

All the chemicals used were of AnalaR grade. Ketorolac tromethamine is available in the market as both tablets and vials. As the tablets contain additives,

pure aqueous standard solutions of the drug were prepared from vials only for the investigations. 5 vials, each of a 30 mg/mL aqueous supply, were carefully emptied into a 50 mL standard flask equipped with a funnel. The empty vials were thoroughly washed several times with water and the washings were also transferred into the standard flask. The funnel was removed after cleaning it to drain the washings into the flask and the contents of the flask were then made up to mark. From this solution, a second stage aqueous stock solution of the drug was prepared in another 25 mL standard flask to get 1mM of the compound.

Buffers of different  $pH$ 's (ionic strength = 0.1 M) were prepared according to literature procedures<sup>2</sup>. Their  $pH$  was measured by an ATI Orion Model 902 Ion Meter under thermostatted conditions ( $25 \pm 0.1^\circ\text{C}$ ). The UV-Visible spectra of the solutions were recorded on a Shimadzu Model UV-160A Ratio Recording Spectrophotometer fitted with thermostatted 1 cm-path-length cuvette holder. The electrochemical measurements such as cyclic voltammetry and differential pulse polarography were recorded on an EG&G PARC Model 264 A3 Polarographic Analyser/Stripping Voltammeter whereas the coulometry was on a BAS Model CV-27 Voltammograph, accessed with an Omniphotic 2001  $\times$ -Y/t Recorder of Digital Electronics. A Carlo-Erba (presently Fisons) Model EA 1108 CHNS-O Elemental Analyser linked with a Sartorius Model MC5 Microbalance, was used for the elemental analysis of the compounds.

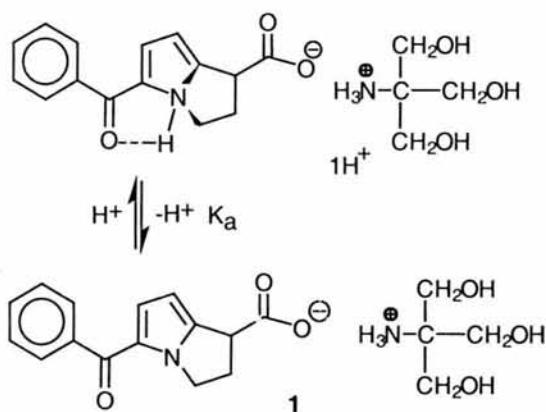
All the spectra were recorded using double walled cuvette holders of the spectrophotometer thermostatted by an Insref model cryostatic circulating liquid

bath with a temperature stability of  $\pm 0.1^\circ\text{C}$ . The cyclic voltammograms and differential pulse polarograms were run on a 6 mL sample solution transferred into the electrochemical cell. Before each run, nitrogen gas was purged for about 4 minutes. Buffer (5 mL) and 1 mL of water were mixed for the blank run while buffer (5 mL) and 1 mL of the sample were mixed for the sample run. For non-aqueous measurements, TEAP in acetonitrile is used as the supporting electrolyte.

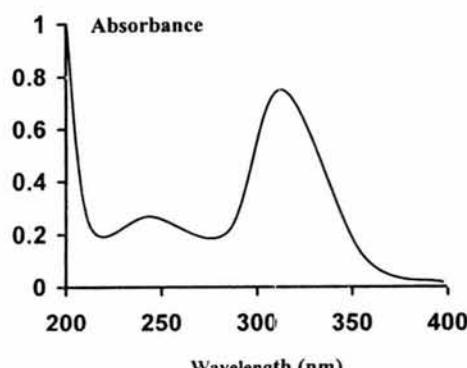
## Results and Discussion

### Spectral studies

The structures of the compound and its protonated form are shown as **1** and **1H<sup>+</sup>** in **Scheme I**. Molecular energy minimisation studies using the software, PCWIN, reveals that the protonated form is stabilised by hydrogen bonding. The aqueous electronic spectrum of **1**, recorded at *pH*=7 is shown in **Figure 1**. The spectral features are near independent of *pH* in



**Scheme I**



**Figure 1**—Electronic spectrum of **1** ( $1 \times 10^{-5} M$ ) at *pH*=7.02

the wavelength region 200-1100 nm, suggesting either that the lone pair of electrons on the pyrrole nitrogen does not participate in the electronic transitions in the wavelength region studied because it becomes part of the aromatic sextet of the pyrrole ring or that the pyrrole nitrogen is hardly protonated because pyrrole is an extremely poor base ( $\text{pK}_a = 0.40$ ). The basicity of the pyrrole moiety might be further reduced due to the presence of the electron-withdrawing carbonyl and carboxy groups nearby. The drug is expected to possess three transitions, viz., the  $\pi \rightarrow \pi^*$  and  $n \rightarrow \pi^*$  transitions of the benzoyl group and the  $\pi \rightarrow \pi^*$  transition from the pyrrole ring.

The highest energy band below 200 nm (which could not be read due to the limitation of wavelength range for the instrument) should be from the benzene ring. The low intense ( $\epsilon = \sim 8500 \text{ lit}^{-1} \text{ mol}^{-1} \text{ cm}^{-1}$ ) band at  $\sim 250$  nm with a negligible shift in position as *pH* varies, is attributed to the  $\pi \rightarrow \pi^*$  transition of the carbonyl group. The moderately intense band ( $\epsilon = \sim 24000 \text{ lit}^{-1} \text{ mol}^{-1} \text{ cm}^{-1}$ ) at  $\sim 320$  nm exhibits a small red-shift in the *pH* range  $0.16 < \text{pH} < 4.00$ . This band may be originating from the  $\pi \rightarrow \pi^*$  transition of the conjugated three double bonds of the pyrrolyl moiety (which includes the carbonyl's double bond). The spectral data of **1**, in the wavelength region 1100-200 nm, are collected in **Table I**.

**Table I**—Electronic spectral data of ketorolac romethamine\*

pH	$\lambda^a (\epsilon)^b$
0.16	317.0 (22,763)
	250.0 (10,630)
4.20	321.6 (23,515)
	249.4 (8,875)
6.50	322.4 (27,576)
	249.4 (9,326)
10.0	322.6 (23,816)
	249.4 (8,473)

a, in nm; b,  $\text{lit}^{-1} \text{ mol}^{-1} \text{ cm}^{-1}$ ; \* in methanol at  $25^\circ\text{C}$

### Electrochemical studies

Organic compounds containing carbonyl group have evinced considerable research interest among electrochemists for the group's versatile electrochemical behaviour with a mechanism that varies with the solvent, *pH*, nature of the electrode material and

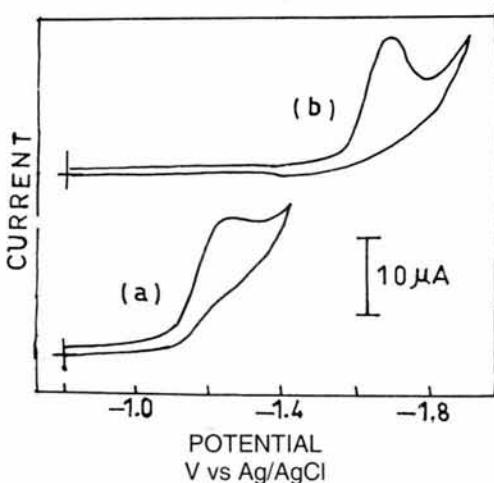


Figure 2—Cyclic voltammograms of **1** ( $1.6 \times 10^{-4} M$ ) on SMDE at pH of (a) 2.20 and (b) 10.02 (scan rate, 50 mV/sec)

other electrochemical experimental conditions<sup>3-6</sup>. Cyclic voltammograms of **1** are exhibited in Figure 2 at two representative pH's. It is clear from these polarograms that the electrochemical behaviour of the drug depends on the pH of the medium. It seems to undergo a single step reversible electron transfer in media of pH below 6.00 and in a two step successive irreversible transfer in those above 6.00. It is further evident from this figure that the reduction peak potentials shift cathodically as the pH increases. This trend suggests the involvement of  $H^+$  ions in the electrochemical reduction step.

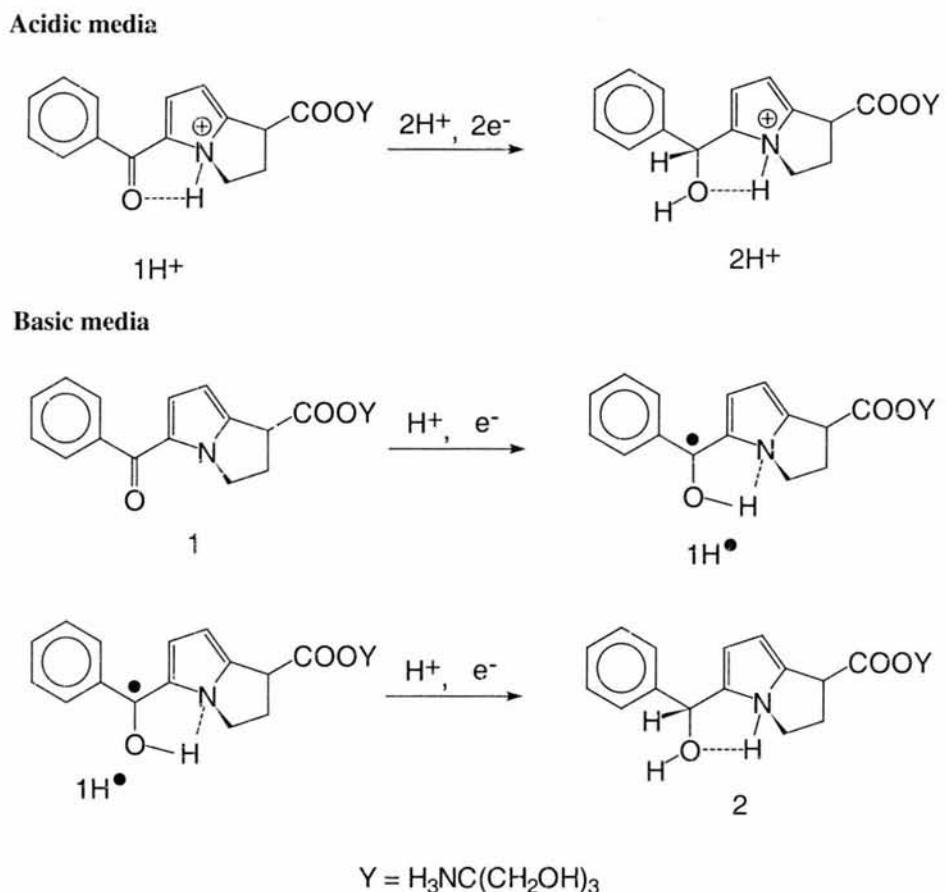
The peak potential,  $E_p$  varies with pH at 25° C as,  $E_p = E_p^0 - m (0.05916/n) pH$  where  $E_p^0$  is the peak potential at a reference pH (activity of  $H^+ = 1$  or  $pH = 0$ ). Hence, a plot of  $E_p$  vs pH should give a straight line from the slope of which one can calculate the number of  $H^+$  ions involved in the electrochemical reduction step, provided, one knows the value of n by coulometry or by other means. Coulometric studies of **1** in several buffers of a wide pH range gave a value of 2 for n when electrolysis was carried out at potentials cathodic to the cyclic voltammetric response. Attempts to measure the number of electrons involved in each of the two reduction peaks in the media of  $pH > 6.00$  were unsuccessful. This suggests that the two peaks correspond to the electrochemical reduction of the same site but in consecutive electron transfer mechanism. The number of electrons, n for any diffusion-controlled peak of cyclic voltammetry can be evaluated from the application of Randles-Sevcik equation,

$$i_p = 2.69 \times 10^5 n^{3/2} A D^{1/2} v^{1/2} c$$

where  $i_p$  is the peak current, A the area of the electrode, D the diffusion coefficient, v the scan rate and c the concentration of the electroactive species<sup>7</sup>. The value of n calculated by this method for **1** was 2 in media of  $pH < 6.00$  and 1 for each of the two reduction steps in basic media. Hence it is assumed that the only reducible site i.e., carbonyl group of **1** undergoes electrochemical reduction through different mechanistic pathways in acid and basic media. Assigning a mechanism to the two-electron single step electrochemical reduction in acid medium involving two  $H^+$  ions is rather straight forward because it is reported that keto groups undergo facile  $2 e^-$ ,  $2 H^+$  reduction to give secondary alcohols<sup>6</sup>. In strongly acidic media, the tertiary nitrogen is protonated, even if it is to a negligible extent. Upon protonation, the -NH- hydrogen is likely to be engaged in hydrogen bonding with the carbonyl oxygen as shown in **1H<sup>+</sup>**. The carbonyl group is more polarised in **1H<sup>+</sup>** than in **1**. Reduction of **1H<sup>+</sup>** is more facile in this medium because of this enhanced polarisation and high concentration of  $H^+$  ions. The proposed mechanism is presented in Scheme II. Plots of  $E_p$  vs pH were linear with a near-uniform slope of 0.1162 in buffers of  $pH < 6.00$  and 0.05982 in those of  $pH > 6.00$ . The number of  $H^+$  ions calculated from these slopes was 2 in acid range and 1 for each of the two peaks in the basic media, further supporting the mechanism of Scheme II.

Usually, the reduction of carbonyl group is irreversible and is complicated with catalytic currents. The free radical intermediate undergoes a chemical dimerisation before the potential for the second electron addition is arrived<sup>8</sup>. One of the best ways of understanding the electrochemical behaviour of carbonyl group is to study the effect of scan rate, v and concentration, c of the compound on its cyclic voltammetric peak current,  $i_p$ . Plots of  $i_p$  vs  $v^{1/2}$  are linear in acid range and slightly non-linear in basic range. As the scan rate increases, the  $i_p$  vs  $v^{1/2}$  plot becomes more linear in basic media. At high scan rates, the intermediate is quickly brought to the second electron transfer potential leaving hardly any time for dimerisation. Relevant electrochemical data obtained from these studies are collected in Table I.

Even though the electronic spectral behaviour of **1** is similar in aqueous and non-aqueous media, its electrochemical response cannot be expected to be so because most of the electrochemically important non-aqueous solvent are aprotic in nature and hence can not yield  $H^+$  ions for reduction. The electrochemical



Scheme II

redox behavior of **1** was examined in non-aqueous solvents such as acetonitrile, dimethyl formamide and dimethyl sulphoxide on stationery mercury drop electrode (SMDE) in the potential region, +0.200 to -2.00 V Vs Ag|AgCl. A typical cyclic voltammogram of **1** in acetonitrile medium on SMDE is shown in Figure 3. Electrochemical reduction of organic compounds in non-aqueous media usually involve participation of the solvent molecules if no other reactive solute is available in the medium<sup>9</sup>. If the non-aqueous medium is very dry, electrochemical mechanism at mercury electrode passes through formation of radical ions. In the case of **1**, an irreversible reduction peak is observed at ~ -0.85 V vs Ag|AgCl. In the reverse scan a sudden adsorption complicated cathodic spike is observed at ~ -0.575 V, followed by a normal anodic peak at ~ -0.40 V. When the cyclic voltammetric cycles are continued, there are two reduction peaks, one at ~ -0.625 V and the other at ~ -0.750 V from the second cycle onwards.

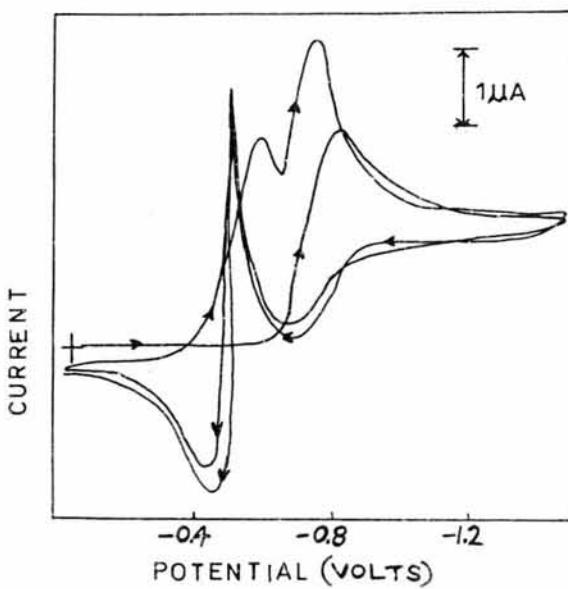
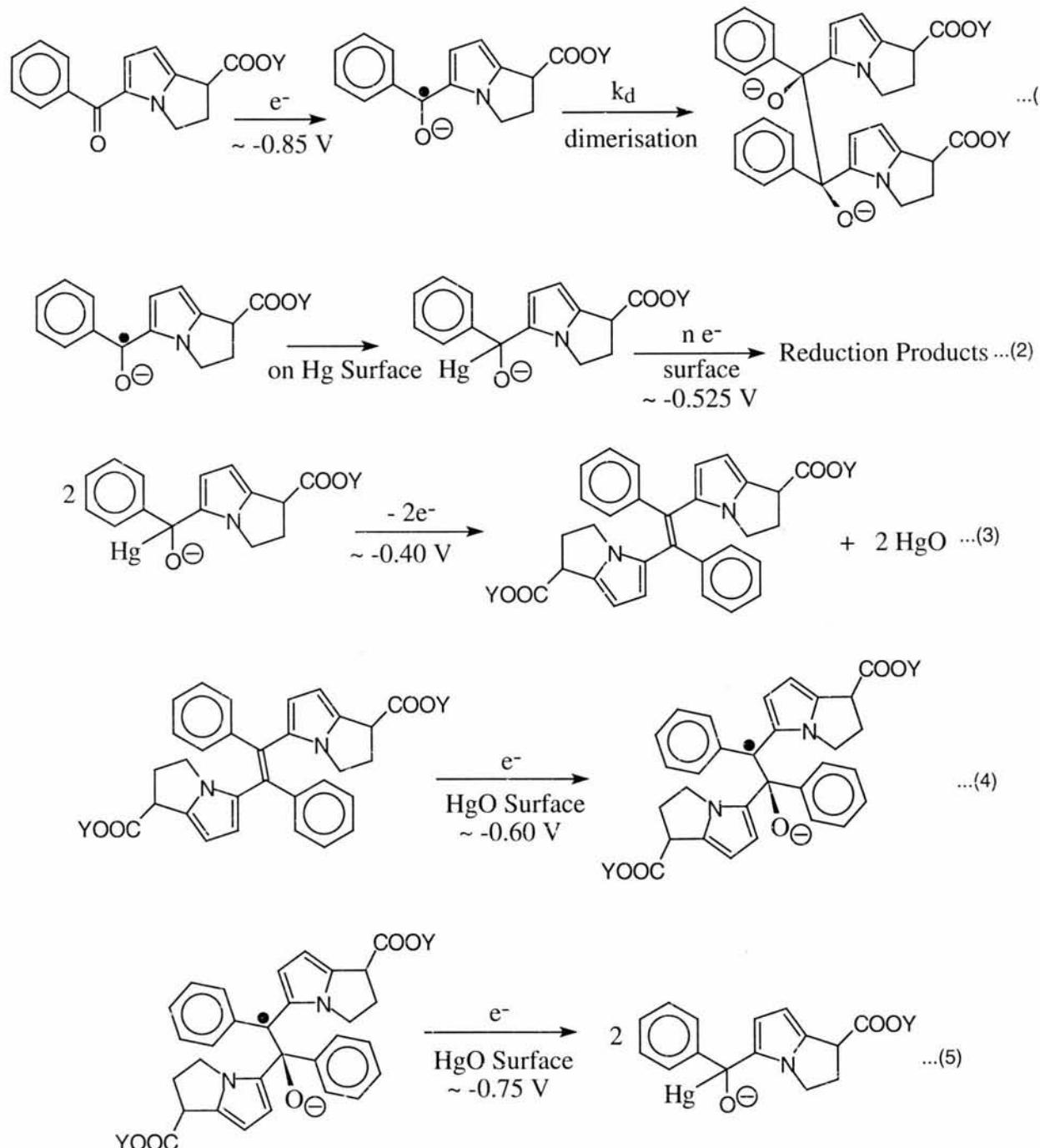


Figure 3—Cyclic voltammograms of **1** ( $1.6 \times 10^{-4} M$ ) on SMDE in acetonitrile with TEAP ( $2 \times 10^{-5} M$ ) as the supporting electrolyte (scan rate, 50 mV/sec)

This spike is repeated in all the subsequent cycles. When a trace quantity of water is added to this medium and the cyclic voltammogram recorded, no such spikes are observed. A plausible mechanism, as shown in **Scheme III** is proposed. A partial proof for this scheme is obtained from controlled potential electrolysis of **1** in acetonitrile on a mercury pool working electrode at  $\sim -1.00$  V vs  $\text{Ag}|\text{AgCl}$ . The

contents of the supernatant acetonitrile solution gave an additional TLC spot below the one expected for **1**. According to **Scheme III**, electrolysis at this potential should result in only the 1,2-diol dianion into solution through the reduction process (1) and the mercuryl anion species on the electrode surface through the surface reaction (2). The other products of **Scheme III** can form only by electrochemical means,



**Scheme III**

triggered by the oxidation of the mercuryl anion species only at (~-0.400 V) a potential anodic to the set controlled potential, -1.000 V. Since this can not happen in controlled potential electrolysis, the other products do not form into solution. Subsequently, the supernatant solution was removed, the electrode compartment was cleaned with pure acetonitrile, filled with fresh acetonitrile blank solution (containing only the supporting electrolyte, tetraethyl ammonium perchlorate) and controlled potential electrolysis was done at ~-0.3000V vs Ag|AgCl. The supernatant solution gave a TLC spot different from those of **1** and the diol anion. According to **Scheme III**, this spot is due to the stilbene derivative generated from reaction (3).

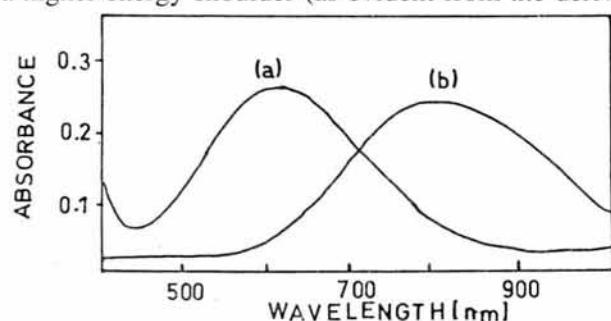
This sort of assignment is similar to that reported for a host of carbonyl compounds in non-aqueous media<sup>6</sup>.

#### Coordination chemistry

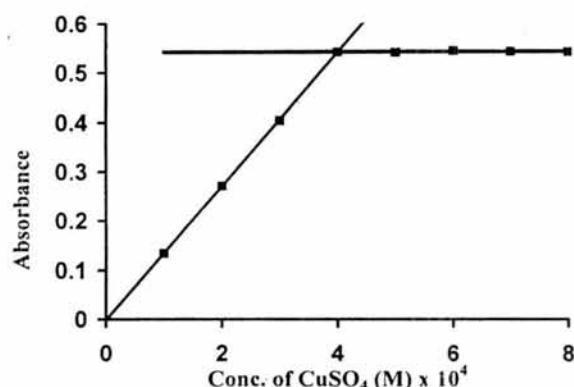
**1** has heterocyclic tertiary nitrogen and suitably positioned carbonyl oxygen and hence is expected to be a potential bidentate ligand. In **Figure 4**, is shown the spectral evidence of complexation between **1** and cupric(II) ion. The d-d transition of the tetraaquacopper(II) ion, observed at ~810 nm, disappears and a new high energy band at ~600 nm is obtained, when **1** is mixed to aqueous copper sulphate solution at a 2:1 molar ratio ( drug to  $\text{Cu}^{+2}$  ). Upon the addition of the drug to the cupric sulphate, the pale blue colour of the copper (II) solution immediately turns deep blue as in the case of addition of ammonia to copper (II) ion.

To assess the metal ligand stoichiometry, a Job's method was adopted. The results shown in **Figure 5**, reveal that the metal to ligand ratio is 1:2.

As the di-ketorolac tromethamine copper(II) complex exhibits a main absorption maximum along with a higher energy shoulder (as evident from the deriva-



**Figure 4**—Overlapped electronic spectra of (a) copper sulphate ( $1 \times 10^{-4} M$ ) and (b) solution containing **1** ( $2 \times 10^{-4} M$ ) and  $\text{CuSO}_4$  ( $1 \times 10^{-4} M$ )



**Figure 5**—Job's plot for  $\text{CuSO}_4$  vs ketorolac tromethamine ( $8 \times 10^{-4} M$ ) at 615 nm

**Table II**—Cyclic voltammetric data of ketorolac tromethamine<sup>†</sup>

Sl. No.	pH	$-E_{pc}$ (V)	$i_{pc}$ ( $\mu\text{A}$ )	$\alpha n_a$	$k_h^0$ ( $\text{cm}^2 \text{s}^{-1}$ )	$D_0 \times 10^6$ ( $\text{cm}^2 \text{s}^{-1}$ )
1	4.2	1.22	0.50	0.46	$5.13 \times 10^{-7}$	6.07
2	5.0	1.28	0.33	0.53	$6.39 \times 10^{-8}$	6.06
3	7.0	1.59	0.55	0.66	$6.67 \times 10^{-9}$	5.62
4	8.0	1.46	0.25	0.67	$7.32 \times 10^{-11}$	5.65
			1.60	0.50	$5.69 \times 10^{-19}$	5.95
5	10.0	1.72	0.65	0.69	$7.68 \times 10^{-13}$	5.40
			1.48	0.27	$6.34 \times 10^{-20}$	5.45
6	11.8	1.55	0.75	0.77	$7.96 \times 10^{-14}$	5.22
			1.75	0.31	$6.96 \times 10^{-20}$	4.90
7	12.9	1.67	0.68	0.64	$8.27 \times 10^{-14}$	4.30
			1.82	0.32	$7.92 \times 10^{-20}$	4.95
8	DMF	0.67	0.41	0.57	$7.4 \times 10^{-9}$	6.19
			0.79	0.72	$6.35 \times 10^{-11}$	6.94
9	$\text{CH}_3\text{CN}$	0.58	0.36	0.63	$8.98 \times 10^{-8}$	6.54
			0.80	0.61	$7.55 \times 10^{-12}$	6.83

<sup>†</sup> at  $25^\circ \text{C}$ , scan rate 50 mV/sec

tive spectrum), a tetragonal pyramidal structure is suggested for the complex with one water molecule occupying the apex position. Structure **3** can be assigned for the complex. Cyclic voltammetric data of betorolac tromethamine is provided in **Table II**.

#### Drug assaying

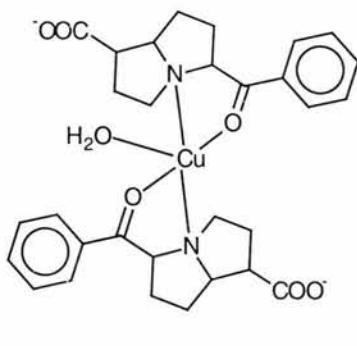
Exploiting the fact that the absorbance of the band at 320 nm is linear to concentration of the drug and that the extinction coefficient is considerably high, a spectrophotometric determination **1** was attempted at an optimum pH of 6.50 and wavelength, 322 nm. **1** could also be readily analysed by differential pulse

**Table III** — Spectrophotometric and differential pulse polarographic assaying data of ketorolac tromethamine in aqueous buffers

Sample	Amount labeled (mg)	Photometry <sup>a</sup>		Polarography <sup>b</sup>	
		Amount recovered (mg)	Recovery (%)	Amount recovered (mg)	Recovery (%)
1	30	28.95	96.50	29.83	99.40
2	30	29.02	96.73	29.72	99.06
3	30	29.12	97.07	29.85	99.50
4	30	28.99	96.63	29.82	99.43
5	30	29.42	98.06	29.96	99.87

<sup>a</sup>, in aqueous media of pH= 6.50 at 322 nm<sup>b</sup>, in aqueous media of pH= 10.00 at SMDE at scan rate 5 mVs<sup>-1</sup>, pulse height

100 mV (first peak) and drop time at 1 sec



polarography in basic aqueous buffers. The assaying data are presented in **Table III**.

#### Acknowledgement

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